Sleep electroencephalographic asymmetry in Parkinson's disease patients before and after deep brain stimulation

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Abstract: Objective Unilateral manifestation of motor dysfunction is a prominent hallmark of Parkinson's disease (PD). We investigated how the motor laterality of the disorder affects sleep neural asymmetry before and after Deep Brain Stimulation (DBS). Methods Twenty-seven PD patients of the akinetic-rigid subtype were studied; 11 with right dominant (RD) and 16 with left dominant (LD) motor symptoms. Neuronal sleep asymmetry was computed as the difference of sleep slow-wave energy (SWE) between left and right hemispheres. We used linear mixed models to assess the relationship between symptomatic profile and SWE asymmetry. Results LD PD patients exhibited frontal electroencephalographic (EEG) asymmetry and motor laterality pre-DBS with increased SWE contralateral to their affected body side, which diminished post-DBS. The RD group did not exhibit neither neural asymmetry nor motor laterality pre- and post-DBS. There was a significant negative correlation between the motor laterality and sleep EEG asymmetry. Conclusions Our results suggest evidence for a local use-dependent modulation of SWE as a result of the lateralized pathological motor profile. More bilateral motor symptoms and optimized treatment contribute to diminished sleep EEG asymmetry. Significance These novel findings about the association between symptomatic motor laterality and sleep neural asymmetry may provide targeted therapeutic insights.

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Sleep electroencephalographic asymmetry in Parkinson's disease patients before and after deep brain stimulation

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HIGHLIGHTS

- There is evidence for local use-dependent neuronal sleep modulation as a result of the lateralized pathological motor profile.
- More bilateral motor symptoms and optimized treatment contribute to diminished sleep EEG asymmetry.
- The association between symptomatic motor laterality and sleep neural asymmetry may provide targeted therapeutic insights.

ABSTRACT

Objective: Unilateral manifestation of motor dysfunction is a prominent hallmark of Parkinson's disease (PD). We investigated how the motor laterality of the disorder affects sleep neural asymmetry before and after Deep Brain Stimulation (DBS).
Methods: Twenty-seven PD patients of the akinetic-rigid subtype were studied; 11 with right dominant (RD) and 16 with left dominant (LD) motor symptoms. Neuronal sleep asymmetry was computed as the difference of sleep slow-wave energy (SWE) between left and right hemispheres. We used linear mixed models to assess the relationship between symptomatic profile and SWE asymmetry.
Results: LD PD patients exhibited frontal electroencephalographic (EEG) asymmetry and motor laterality pre-DBS with increased SWE contralateral to their affected body side, which diminished post-DBS. The RD group did not exhibit neither neural asymmetry nor motor laterality pre- and post-DBS. There was a significant negative correlation between the motor laterality and sleep EEG asymmetry.
Conclusions: Our results suggest evidence for a local use-dependent modulation of SWE as a result of the lateralized pathological motor profile. More bilateral motor symptoms and optimized treatment contribute to diminished sleep EEG asymmetry.
Significance: These novel findings about the association between symptomatic motor laterality and sleep neural asymmetry may provide targeted therapeutic insights.

1. Introduction

Slow-wave activity (SWA; electroencephalographic (EEG) power in the delta frequency range 1–4.5 Hz) is the hallmark brain activity of deep sleep and reflects sleep depth and sleep need regulation (Achermann and Borbély, 2003). It is already established that SWA can be regulated locally, in an activity-dependent manner. SWA increases as a function of prior use and neuronal plasticity (Esser et al., 2006; Huber et al., 2007; Tononi and Cirelli, 2014). Specifically, increased synaptic activity due to motor learning can selectively induce SWA in the previously activated cortical region (Huber et al., 2004). Conversely, lack of activity after arm immobi-

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lization during the day leads to a local decrease of SWA over the contralateral motor cortex (Huber et al., 2006). Furthermore, slow-wave energy (SWE; cumulative SWA throughout a sleep episode) reflects total sleep need dissipation (Borbély, 1982; Achermann and Borbély, 1990; Achermann et al., 1993; Werth et al., 1996). SWE has been shown to be locally expressed as well (Maric et al., 2017).

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder owing primarily but not only to dopaminergic denervation of the striatum leading to excessive abnormal synchronization of neuronal activity in basal ganglia-cortical loops (Hammond et al., 2007). This pathological synchronization is thought to be inextricably linked to PD clinical phenotype characterized by akinesia, muscle rigidity, postural instability and (resting) tremor. Treatments of PD include pharmacological approaches, typically dopaminergic agents, and surgical therapies as e.g. deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the globus pallidus internus (Armstrong and Okun, 2020).

A prominent distinctive pathological hallmark of PD is the asymmetry of dopaminergic neurodegeneration at its onset, accompanied by a characteristic unilateral manifestation of motor dysfunction (Riederer et al., 2018). Asymmetry was shown to become less prominent over the disease course (Nandhagopal et al., 2009), while side of disease onset and progression of motor impairment are not entirely independent from each other (Baumann et al., 2014). Despite the impressive and poorly understood asymmetrical nature of PD and the vast work on the subcortical level, very few studies have investigated the potential neural asymmetries of PD patients on a cortical level (Pollok et al., 2012; Hall et al., 2014; Heinrichs-Graham et al., 2017). However, these studies were focused on the investigation of motor-cortical oscillations (i.e., beta oscillations) in PD during wakefulness.

There is growing awareness of the bidirectional relationship between sleep and PD. Schreiner and colleagues found an association between higher SWE and slower motor progression (Schreiner et al., 2019). Amato and colleagues showed that increased actigraphy-based total sleep time was related to reduced motor impairment (Amato et al., 2018). To our knowledge, no study to date has investigated the association between symptomatic motor laterality and sleep neural asymmetry. In this work, we hypothesized a symptomatic use-dependent modulation of the sleep EEG neural pattern in PD patients. We investigated how both neural asymmetry and motor laterality of the disorder are affected before DBS and under the optimized therapy of DBS, which should diminish neuronal asymmetry. We differentiate between PD patients with left-sided onset and right-sided onset of motor symptoms.

2. Methods

This is a retrospective analysis of a subgroup of patients from an observational controlled trial to examine effects of STN-DBS on sleep–wake behavior in PD (for details see Baumann-Vogel et al., 2017). Here we focused on PD patients of the akinetic-rigid subtype (the biggest subgroup of the trial) as tremor dominant subtypes may modulate the sleep EEG neural pattern differently. The study protocol was approved by the local ethics committee (KEK-ZH-Nr.2013-0360), and written informed consent was given by participating patients. The study has been carried out in accordance with the Helsinki Declaration of 1975.

2.1. Patients

We analyzed data of 27 PD patients who suffer primarily from akinesia and rigidity (AR subtype) and not from tremor and who were treated with bilateral STN-DBS. The PD patients were divided into two groups according to their motor symptom laterality profile; patients with right-sided onset of motor symptoms belong to the right dominant (RD, n = 11, 2 females) group, and patients with left-sided onset of motor symptoms were classified left dominant (LD, n = 16, 7 females). All patients were right-handed.

2.2. Clinical assessment

Patients were examined twice, 3–6 months prior to surgery and 6 months after implantation of DBS electrodes and the bilateral STN-DBS. More details on all assessments can be found in Baumann-Vogel et al., 2017. Briefly, we examined motor outcomes with part III of the Unified Parkinson's Disease Rating Scale (UPDRS). Before DBS, we assessed motor symptoms during an L-dopa challenge test once in the off state and once at L-dopa peak dose (Saranza and Lang, 2020). After STN-DBS, UPDRS assessments were performed again in an ON state (on stimulation in combination with medication). To assess motor laterality in the PD patients, we used lateral motor sub-scores of the UPDRS III. We computed a motor laterality index (MLI) by calculating the ratio of the difference of the right (R) and left (L) motor sub-scores over their sum $((R - L)/(R + L))$ (Kaasinen, 2016). Negative values of the laterality score indicated dominant left side symptoms; positive scores indicated dominant right side symptoms.

2.3. Whole-night PSG/EEG

Digital video polysomnography (PSG) recordings were performed (Embla N7000, RemLogic v3.2) using six electrodes (2 frontal, 2 central and 2 occipital) according to AASM standard criteria (Berry et al., 2015). Sleep stage scoring (30-second epochs) was done by sleep specialists very carefully and with additional standardized considerations as thoroughly described in Baumann-Vogel et al. (2017).

2.4. EEG analysis

Pre-processing of the EEG signal included initially the re-referencing of all electrodes to linked mastoids. The re-referenced EEG signal was zero-phase high-pass filtered at 0.1 Hz and low-pass filtered at 40 Hz. The filtered signal was decomposed in the frequency domain using the Welch's method and power spectra were computed for each 30-second epoch based on averaging of six 5-second windows using Hanning windowing. A semi-automatic procedure was used for artefact-correction based on power thresholds in the low (0.75–4.5 Hz) and high (20–30 Hz) frequency ranges. SWA was computed as the EEG power between 1 and 4.5 Hz. SWE was computed as the integral of the SWA throughout the night, in that way both the amount of SWA as well as the duration of consolidated non-rapid eye movement (NREM) sleep (sleep stages N2 + N3) are taken into account for the assessment of total sleep need dissipation. Global SWE was computed as the average SWE across all electrodes. EEG asymmetry was computed the same way as the MLI, namely, the ratio of the difference of SWE between right and left electrodes over their sum $((R - L)/(R + L))$ for the three cortical regions; frontal, central and occipital. A positive value of the laterality score indicated higher SWE over the right brain side; a negative value indicated a higher SWE over the left brain side. Analysis was performed in MATLAB (R2017b, The Math-Works, Inc., Natick, Massachusetts, USA).

2.5. Statistical analysis

We used Shapiro-Wilk tests to test for normally distributed data. In case of normally distributed data, we used Student's t-

tests for post hoc comparisons. When not normally distributed, Wilcoxon's rank-sum post hoc tests were used (we report descriptive values of mean and standard error of the mean for normally (i.e., mean ± sem) and median and interquartile range values (i.e., median ± iqr) for not normally distributed data). For correlation analysis, we applied the non-parametric Spearman test. We used linear models (LM) and linear mixed models (LMM) to describe the data. We applied F-test statistics for the description of goodness of fit of the LM and Wald Chi-squared test statistics for the description of goodness of fit for the LMM. For the LMM the patient was treated as the random variable (varying in the intercept) and we used the maximum likelihood method for the estimation of the significant effects. We assessed the LM and LMM variable selection using bidirectional stepwise regression according to the Akaike Information Criterion (AIC) for model comparison. The stepwise principle for model construction is an automatic procedure of selecting the regression model that best describes the data. Initially, all the candidate predictive variables were included in the description of the model and then a mathematical procedure was used in order to estimate the final model that included the variables and/or their interactions that explained best the variation of the outcome. Briefly, an initial model was defined only by the intercept. At a next step, the predictor that best predicted the outcome was selected according to highest correlation with the outcome. If this predictor improved the ability of the model to predict the outcome, then this predictor was retained in the model. Each time a predictor was added, a removal test was made of the least useful predictor. The procedure searched for a second predictor by using semi-partial correlations with the outcome as a criterion. At each step the resulting models were compared to each other using the AIC which was computed as AIC = −2(log-likeli hood) + 2k, where k was the number of model parameters including the intercept and the log-likelihood was a measure of model fit. The lower the AIC the better the fit of the model. The advantage of this method is that it provides an objective way to estimate the LM and LMM based on mathematical criteria. Analysis was performed in R-3.5.1.

3. Results

3.1. Clinical and sleep characteristics of PD patients pre- and post-DBS

The two motor asymmetry groups (LD, RD) did not show any differences regarding mean age (LD: 59.81 ± 2.56 years, RD: 62.8 2 ± 2.56 years, t(24.13) = −0.84, p = 0.41), disease duration (LD: 11.88 ± 0.98 years, RD: 12.45 ± 1.63 years, t(17.12) = −0.31, p = 0.76) and disease stage-indicating Hoehn & Yahr values (Hoehn and Yahr, 1967) (LD: 2 ± 0.5, RD: 2.5 ± 0. 5, W = 75.5, p = 0.52).

Table 1 summarizes motor impairment, dopaminergic medication and PSG sleep stage findings in the two groups before and after STN-DBS. Motor assessment in off stage showed similar high UPDRS III scores in both groups (t(24.9) = 0.63, p = 0.53). Mean score of UPDRS III at L-dopa dose peak improved in both groups (LD: −28.3 ± 3.3, p < 0.001, RD: −20.6 ± 2.8, p < 0.001), however, after a between-group comparison, we found that the RD group was more severely affected compared to the LD group (Figure S1). The mean UPDRS III values following DBS treatment did not show any significant differences when comparing between the two conditions for the two groups. The L-dopa equivalent dose was more reduced following DBS treatment in the LD group (LD: −63.6%±6.11%, p < 0.001, RD: −56.23%±9.1%, p = 0.003). Calculation of sleep parameters before and after DBS showed a decrease of waking time after sleep onset (WASO) after DBS treatment for the LD group (p = 0.048) but not for the RD group, while number of awakenings did not differ. There was also an increase of post-DBS total sleep time (TST) for the RD group (p = 0.042) but not for the LD group. The rest of the sleep parameters did not show any significant differences when comparing between the two conditions for the two groups. These differences in WASO and TST for the LD and RD group, respectively may be explained by analogous changes in NREM and REM duration, which are not significant probably due to high data variability. Nevertheless, when summed up together they lead to the respective significant changes in WASO and TST.

3.2. Global SWE: Pre-DBS comparison between LD and RD group

In a first step, the SWE averaged across all electrodes was compared between the two groups. A simple linear model (Table S1) was calculated to predict patients' whole-night, global SWE based on their age and group of motor asymmetry (LD or RD). A significant regression equation was found (LM: F(3,22) = 6.97, p = 0.002), with an R^2 of 0.417. Motor asymmetry group (b = −224, p = 0.043) and age (b = −3.75, p = 0.001) of the patient were significant predictors of the resulting global SWE with the LD group exhibiting a trend for higher SWE compared to the RD group (t(21.22) = 1.84, p = 0.08, mean ± sem: LD: 75.72 ± 14.61 mV^2, RD: 44.95 ± 8.17 mV^2) (Fig. 1B). Because of the significant age effect, the data was split by the median (62 years) into two age groups for each of the asymmetry groups (LD and RD), however, no significant differences in SWE were found between the age groups (LD: W = 45, p = 0.06, RD: t(6.06) = 0.12, p = 0.908.

3.3. Global SWE: Post-DBS changes in both LD and RD groups

In a next step, we investigated the changes in global SWE after DBS. The stepwise LMM approach (Table S2) showed that whole-night, global SWE was affected by DBS ($\chi^2(1)$ = 9.59, p = 0.002, b = 20.4, se (standard error) = 6.94) and age ($\chi^2(1)$ = 26.05, p < 0.001, b = −3.89, se = 0.72). There was also a significant group by age interaction effect ($\chi^2(1)$ = 7.03, p = 0.008, b = 3.26, se = 1.29) on the resulting SWE. The data was split again by the median into two age groups and no differences in the SWE increase were found between the age groups in neither asymmetry group (LD: t(11.96) = −0.29, p = 0.78, RD: t (8) = 0.06, p = 0.96). The LD group showed a significant SWE increase post-DBS (t(13) = 3.14, p = 0.008, 47.52 ± 15.15 %). Also, the RD group exhibited a significant SWE increase after the treatment (t(9) = 3.32, p = 0.009, 75.69 ± 22.77 %), with no difference in mean global SWE increase between the two groups (t(16.5) = −1.03, p = 0.32) (Fig. 2, highlighted boxplots).

3.4. Local changes of SWE

In order to investigate local aspects of SWE in the PD patients, a LMM (Table S3) was computed taking into account regional changes in SWE (frontal (F), central (C), and occipital (O)). The stepwise LMM approach revealed that DBS ($\chi^2(1)$ = 4.93, p = 0.026, b = 17.69, se (standard error) = 6.56), age ($\chi^2(1)$ = 23.16, p < 0.0001, b = −3.53, se = 0.51), cortical area (i.e., locality) ($\chi^2(2)$ = 256.35, p < 0.0001, b_{FvsC} = −83.84, se = 20.18, b_{FvsO} =-−165.41, se = 20.18) and group of motor asymmetry ($\chi^2(1)$ = 6.34, p = 0.012, b = −149.17, se = 53.17) were significant predictors of changes in SWE. There was also a significant age by locality interaction ($\chi^2(2)$ = 44.62, p < 0.001, $b_{age:FvsC}$ = 1.15, se = 0.32, $b_{age:FvsO}$ = 2.08, se = 0.32), DBS by locality interaction ($\chi^2(2)$ = 6.74, p = 0.034, $b_{DBS:FvsC}$ = −3.05, se = 6.13, $b_{DBS:FvsO}$ =-−14.57, se = 6.13) and group by age interaction ($\chi_2(1)$ = 6.67, p = 0.01, b = 2.12, se = 0.85) revealed by the LMM. Statistical comparisons revealed that for the LD group SWE increase was signifi-

Table 1
Unified Parkinson's Disease Rating Scale (UPDRS) part III assessments, dopaminergic medication equivalent dose and sleep parameters for left dominant and right dominant PD groups pre- and post-DBS. Mean ± standard error of the mean. Abbreviations: LED, levodopa equivalent dosage; DBS, deep brain stimulation; OFF, off state; ON, on state; PSG, polysomnography; TST, total sleep time; SL, sleep latency to N2; N1-3, non-rapid eye moment (NREM) sleep stages 1–3; REM, rapid eye movement sleep; WASO, wake after sleep onset; nWASO, number of awakenings after sleep onset; SEFF, sleep efficiency. Unit abbreviations: mg, milligrams; min, minutes; #, number; %, percentage.

	Left Dominant			**Right Dominant**		
	Pre DBS	**Post DBS**	**p-value**	**Pre DBS**	**Post DBS**	**p-value**
UPDRS III OFF	44.7 ± 3.8	–	–	41.6 ± 2.9	–	–
UPDRS III ON	16.4 ± 1.41	16.7 ± 1.6	0.9	21.1 ± 1.8	18.2 ± 1.5	0.17
LED total (mg)	1134.2 ± 91	432.3 ± 88.2	**<0.001**	1070.5 ± 171	420.4 ± 126.8	**0.003**
PSG sleep stages						
TST (min)	319.6 ± 20.4	336.2 ± 21.3	0.313	255.2 ± 19.2	302 ± 26.7	**0.042**
SL (min)	20.5 ± 5.4	24.5 ± 5.9	0.518	45 ± 14.9	31.7 ± 7.8	1
NREM (min)	271.5 ± 17.1	279.5 ± 14.6	0.379	222.3 ± 18.2	264.5 ± 21.9	0.054
N1 (min)	68.3 ± 13.0	68.5 ± 7.3	0.877	62.4 ± 11.0	74 ± 12.4	0.32
N2 (min)	158.8 ± 11.0	151.4 ± 11.2	0.571	123.6 ± 14.1	140.9 ± 15.3	0.32
N3 (min)	44.4 ± 9.4	59.5 ± 9.7	0.155	36.3 ± 10.5	49.6 ± 10.9	0.147
N2 + N3 (min)	203.2 ± 16.3	210.9 ± 15.6	0.68	159.9 ± 16.1	190.6 ± 21	0.28
REM (min)	48.1 ± 6.7	56.8 ± 8.6	0.535	32.9 ± 10.1	37.5 ± 8.2	0.557
WASO (min)	104.4 ± 15.4	81.2 ± 15.2	**0.048**	128.9 ± 10.6	101.9 ± 25.6	0.122
nWASO (#)	50.6 ± 9	45.3 ± 6.3	0.979	46.2 ± 6.5	40.4 ± 4.1	0.288
SEFF (%)	72.3 ± 4.4	76.4 ± 4.3	0.088	59.8 ± 4.4	70.1 ± 6.4	0.083

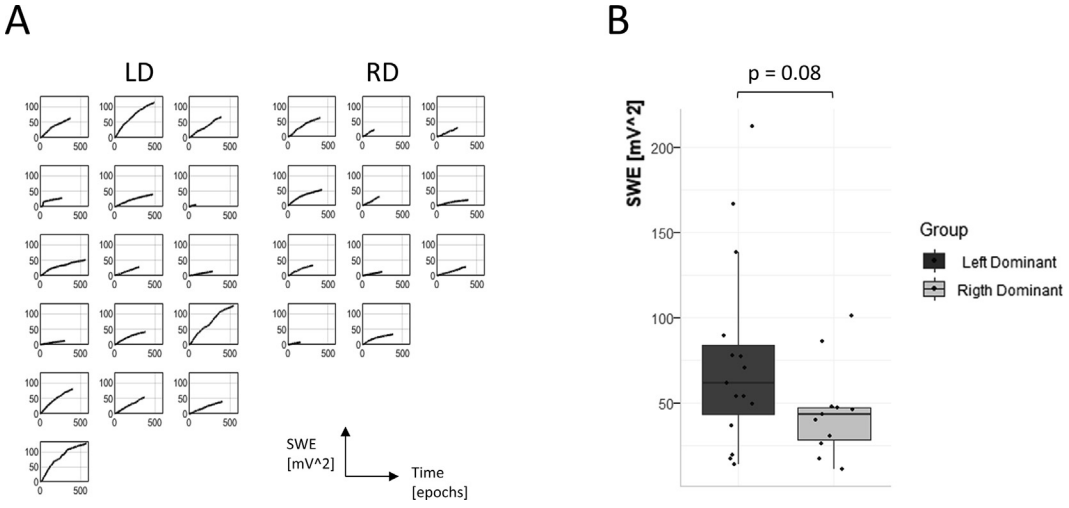

Fig. 1. (A) Individual global slow-wave energy (SWE) traces for both groups (LD, left dominant; RD, right dominant) throughout the night before deep brain stimulation (pre-DBS). Accumulated slow-wave activity (SWA) over time (all non-rapid eye movement (NREM) stages N2 and N3 episodes). (B) Boxplot showing total sleep need dissipation for the LD and the RD group before DBS treatment.

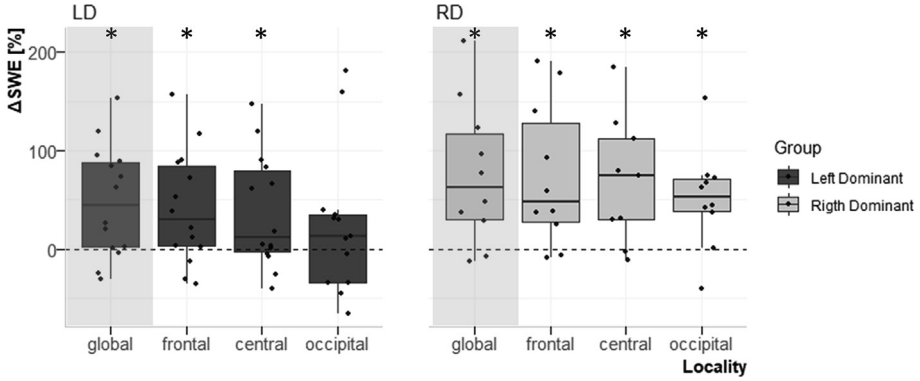

Fig. 2. Increase in slow-wave energy (ΔSWE) after deep brain stimulation (DBS) treatment for both asymmetry groups (LD, left dominant; RD, right dominant) on the global and on the local (frontal, central and occipital) level. Asterisks denote statistical significance of SWE increases (global and local changes, $p < 0.05$).

cant in the frontal and central cortical sites, but not in the occipital one (frontal: $t(13) = 2.68$, $p = 0.02$, central: $t(13) = 2.4$, $p = 0.03$, occipital; $t(12) = 1.19$, $p = 0.26$), while the RD group showed significant increases in all cortical sites (frontal: $t(9) = 3.22$, $p = 0.01$, central: $t(8) = 3.22$, $p = 0.01$, occipital: $t(9) = 3.2$, $p = 0.01$). Local SWE changes are illustrated in (Fig. 2).

3.5. Left-right sleep EEG asymmetry

Next, we computed the left–right asymmetry of SWE for the three recorded cortical regions; frontal, central and occipital. No asymmetry was evident for the central and occipital regions for the two groups in neither of the two conditions (e.g., pre- and post-DBS) (Figure S2). The stepwise LMM approach (Table S4) showed a significant effect of DBS treatment ($\chi^2(1) = 6.48$, $p = 0.01$, $b = -0.031$, se (standard error) = 0.013) on the frontal SWE asymmetry (i.e., frontal SWE asymmetry diminishes after DBS) and a trend in the group effect ($\chi^2(1) = 3.42$, $p = 0.064$, $b = -0.032$, se = 0.02) (i.e., trend for less frontal SWE asymmetry for the RD group). No age effect was evident after stepwise regression. Before treatment, the LD group exhibited frontal SWE asymmetry ($t(14) = 2.33$, $p = 0.035$, 0.031 ± 0.013) with the left cortical side showing less SWE than the right cortical side, while the RD group did not show any asymmetrical SWE ($t(10) = -0.88$, $p = 0.4$, -0.016 ± 0.018). A direct comparison of the asymmetry between the two groups revealed that they differed in their asymmetrical sleep EEG activity ($t(19.66) = 2.1$, $p = 0.049$) (Fig. 3A). After DBS treatment, both the LD group and the RD group did not exhibit any asymmetry in SWE (LD: $t(14) = -0.83$, $p = 0.42$, -0.012 ± 0.014, RD: $t(9) = -1.67$, $p = 0.13$, -0.029 ± 0.017) and also no difference between their mean SWE asymmetry ($t(19.12) = 0.79$, $p = 0.44$) (Fig. 3A). In-group comparisons showed a significant difference between pre- and post-DBS SWE asymmetry for the LD group ($t(13) = 3.15$, $p = 0.008$), but not for the RD group ($t(9) = 0.5$, $p = 0.63$) (Fig. 3A).

3.6. Clinical outcome linked to frontal sleep EEG asymmetry

To test whether the SWE asymmetry in the frontal electrodes was associated with the clinical outcome after DBS, we applied the stepwise LMM approach on the motor laterality index (MLI) (Table S5) which revealed that group of asymmetry ($\chi^2(1) = 10.96$, $p = 0.001$, $b = -0.47$, se (standard error) = 0.13) was a significant predictor for the MLI (i.e., less motor laterality for the RD group), while there was a trend in the DBS effect ($\chi^2(1) = 3.39$, $p = 0.07$, $b = -0.3$, se = 0.12) and the group by DBS interaction ($\chi^2(1) = 3.53$, $p = 0.06$, $b = 0.33$, se = 0.19). Before DBS treatment the LD group exhibited significant motor laterality ($t(15) = 4.85$, $p < 0.001$, 0.4 ± 0.08) with the patients showing more severe motor symptoms on their left body side while the RD group did not show such motor symptom laterality ($t(10) = -0.32$, $p = 0.75$, -0.02 ± 0.05). The two groups differed significantly in their pre-DBS MLI ($t(22.44) = 4.4$, $p < 0.001$) (Fig. 3B). On DBS treatment, both groups had diminished motor laterality (LD: $t(15) = 1.17$, $p = 0.26$, 0.11 ± 0.1, RD: $t(10) = 0.08$, $p = 0.94$, 0.01 ± 0.1) with no differences between the groups ($t(22.88) = 0.72$, $p = 0.48$) (Fig. 3B). In-group comparisons showed a significant difference between pre- and post-DBS MLI for the LD group ($t(15) = 2.44$, $p = 0.028$), but not for the RD group ($t(10) = -0.2$, $p = 0.84$) (Fig. 3B). Moreover, a negative correlation was found between MLI and frontal SWE asymmetry before the DBS treatment when the two groups are pooled ($n = 26$, $r_s = -0.5$, $p = 0.011$), however, there was no such correlation between laterality in motor symptoms and SWE asymmetry post-DBS ($n = 25$, $r_s = 0.17$, $p = 0.43$) (Fig. 3C).

4. Discussion

The overall aim of this work was to identify asymmetries in the sleep EEG in akinetic-rigid PD patients before DBS and under optimized treatment after DBS surgery. The two prominent PD symptomatic profiles in respect to left and right motor symptom dominance were analyzed separately. Before focusing on the asymmetry, we carefully assessed the background differences in SWE between the groups and found that pre-DBS the RD group exhibited a trend for lower SWE compared to the LD group. Taking into account the higher motor severity of the RD group pre-DBS, this observation is in accordance with the results of Baumann et al. (2014) showing an association between right–side akinetic-rigid patients and faster disease progression (Baumann et al., 2014) in combination with the results of Schreiner et al. (2019) who showed that lower SWE also relates to faster disease progression (Schreiner et al., 2019). Succeeding DBS treatment, both groups showed an increase in global SWE, as it has been shown by Baumann-Vogel and colleagues before (Baumann-Vogel et al., 2017). Altered sleep architecture (Table 1) following DBS treatment could be a possible confounder for our observation. SWE increase from the two groups seem to have different profiles. LD PD patients deepened NREM sleep, whereas RD PD patients consolidate sleep by increasing total sleep time resulting in more time to accumulate SWE. Our results suggest different neurophysiological responses to PD depending on the grade of motor severity. Here the RD PD patients had higher pre-DBS UPDRS III scores.

Following our hypothesis for a local use-dependent modulation of SWE reflecting the lateralized motor pathology of the patients, we investigated the sleep EEG asymmetry in the three cortical regions; frontal, central and occipital. Indeed, neural asymmetry was only evident locally in the frontal cortex. A correlational analysis revealed a correlation between the motor laterality index and sleep EEG asymmetry, namely the more prominent the motor laterality the more evident the sleep EEG asymmetry. LD PD patients exhibited significant EEG asymmetry pre-DBS with the more affected side (i.e., right frontal cortex) showing higher SWE compared to the less affected side (i.e., left frontal cortex). They also showed significant motor lateralization with more severe motor symptoms on their left body side. This observation could be evidence for a local use-dependent modulation of SWE as a result of the lateralized pathological motor profile of akinetic-rigid PD patients. Previous studies (in healthy subjects) have shown that excessive synaptic activity due to motor learning locally increases SWA activity in the respective cortical region (Tononi and Cirelli, 2014) and, conversely, reduced synaptic activity due to immobilization causes local SWA decrease (Huber et al., 2004). Nevertheless, it is worth mentioning that rigidity and/or bradykinesia in akinetic-rigid PD patients does not simulate immobility in healthy population, but is rather expressed with difficulties in movement initiation (hence more "training" or force demand on the affected side) due to its neurodegenerative origin. In contrast to the LD group, the RD group did not exhibit neither neural asymmetry nor motor laterality pre-DBS. A possible reason why we observed no asymmetry in akinetic-rigid patients with right-sided onset of motor signs could be that this group typically shows a more rapid progression of motor symptoms compared to LD patients (Baumann et al., 2014), hence, symptoms become bilateral. Another possible explanation for this observation could be framed under the concept of impaired control of habitual behavior (e.g., spontaneous, over-trained motor control) and a shift to goal-directed behavior (e.g., novel, computationally more intensive motor control) in the Parkinsonian state (Redgrave et al., 2010; Bichsel et al., 2018). Moreover, in our cohort all the PD patients in both groups were right-handed. Hence, it would require greater and more intensive effort for the RD patients to perform their habitual right-hand movements compared to the LD patients. Interestingly, it has also been shown that there is a unique correlation between PD symptomatic profile and asymmetry of beta activity (i.e., motor-cortical oscillations) in the wake state during right-hand movement, such that LD PD patients show more left-lateralized (i.e.,

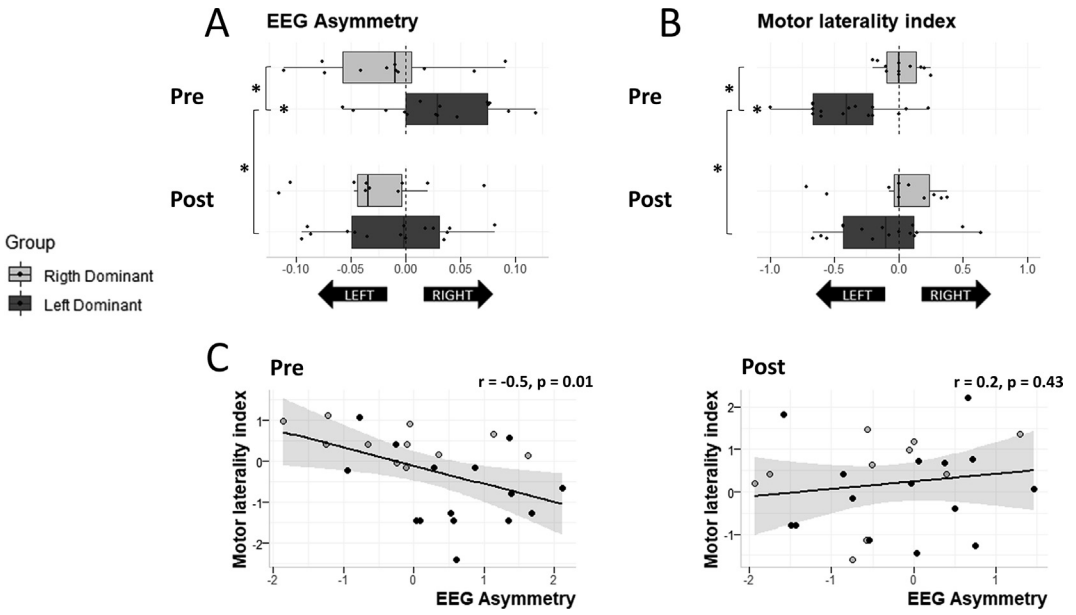

Fig. 3. (A) Frontal sleep electroencephalographic (EEG) asymmetry for both groups (LD, left dominant; RD, right dominant) before and after deep brain stimulation (pre- and post-DBS). Positive values indicate higher slow-wave energy (SWE) on the right hemisphere and negative values indicate higher SWE on the left hemisphere. (B) Motor laterality index for both groups pre- and post-DBS. Positive values of the motor laterality index indicate more severe motor symptoms on the right body side of the Parkinson's disease (PD) patients and negative values of the motor laterality index show increased motor severity of the left body side. (C) Correlation (r, Spearman correlation coefficient; p, statistical significance, grey area, 95% confidence intervals) between motor laterality index (z-scores) and sleep EEG asymmetry (z-scores) for both groups pre- and post-DBS. Asterisks denote statistical significance between pre/post-DBS comparisons and group comparisons, respectively ($p < 0.05$).

contralateral to movement) beta response. Conversely, RD PD patients exhibit more right-lateralized (i.e., ipsilateral to movement) beta response (Heinrichs-Graham et al., 2017). This "redirection" of activity to the healthy hemisphere during right-hand movement execution in RD patients in combination with the more demanding and intensive neuronal plastic processes underlying goal-directed movements might increase the homeostatic drive resulting in higher SWE and thus masking the SWE asymmetry during sleep. After DBS treatment neural asymmetry and motor laterality indices diminished for both groups, hence, no correlation between these two was evident anymore. The effective DBS treatment and clear reduction of the unilateral manifestation of motor dysfunction may account for the diminished neural and motor symptom asymmetry. On the other side, EEG asymmetry effects could have been more prominent when patients would have been in the "off-state" since the dopaminergic treatment may mask motor laterality and EEG asymmetry (Table 1). Moreover, dopaminergic neurotransmission in striatum, the target of levodopa-based therapy in PD, plays also an important role in healthy brain functioning including the circadian rhythms and sleep (Videnovic and Golombek, 2017). Whether asymmetry of dopaminergic neurotransmission may affect the sleep-wake circuit directly leading to sleep EEG asymmetry and/or only indirectly through their motor symptoms in a use-dependent manner remains open. As dopamine primes the brain for enhanced vigilance one could speculate that lateralized dopaminergic dysregulation might result in direct sleep EEG asymmetry in PD.

The small sample size and the few EEG channels are limitations and a larger study, and a higher EEG resolution would be needed to confirm these results.

Nevertheless, we were still able to show a relationship between motor laterality and SWE asymmetry as well as differences between the two groups and optimized treatment. Thus, the importance of taking patient symptom heterogeneity into consideration towards more personalized treatment is highlighted.

5. Conclusion

Our study was the first to assess any relationship between symptom laterality and sleep EEG asymmetry in PD patients. We were able to show a relationship between motor laterality and SWE asymmetry, differences between the two groups according to their motor laterality and differences after optimized treatment. Further experimental sleep modulation studies need to be performed in order to elucidate the causal relationship between sleep and motor symptoms in PD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.12.027.

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